Veno-venous Extracorporeal CO_2 Removal: Can We Reduce Dependence on Mechanical Ventilation During En-route Care?

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ABSTRACT

Background

Casualties with lung failure are mechanically ventilated during aero-medical evacuation to the continental USA. Positive-pressure mechanical ventilation is potentially injurious to the lung. Consequences of contemporary lung-protective strategies may include cardiovascular instability, use of high fraction of inspired O_2, hypoventilation, hypercarbia, and acidosis. These effects may complicate patient management,

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14. ABSTRACT
Casualties with lung failure are mechanically ventilated during aero-medical evacuation to the continental USA. Positive-pressure mechanical ventilation is potentially injurious to the lung. Consequences of contemporary lung-protective strategies may include cardiovascular instability, use of high fraction of inspired O2, hypoventilation, hypercarbia, and acidosis. These effects may complicate patient management, motivating a search for better lung-replacement approaches. We investigated the ability of a novel extracorporeal veno-venous CO2 removal (V2CO2R) device to reduce minute ventilation (MV) while maintaining normocarbia. Our goal was to explore the potential utility of this technology to reduce dependence on mechanical ventilation during en-route care.

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motivating a search for better lung-replacement approaches. We investigated the ability of a novel extracorporeal veno-venous CO_2 removal (V_2CO_2R) device to reduce minute ventilation (MV) while maintaining normocarbia. Our goal was to explore the potential utility of this technology to reduce dependence on mechanical ventilation during en-route care.

Methods

Seven healthy swine underwent tracheostomy, volume-controlled mechanical ventilation, and 72 hours of sedation and round-the-clock ICU care. After a 20 u/kg heparin bolus, a 15 Fr. dual-lumen catheter was inserted in the external jugular vein, advanced to the superior vena cava, and connected to the Hemolung, an extracorporeal pump-driven V_2CO_2R device. MV was titrated downwards to maintain normocarbia ($PaCO_2$ 35-45 mm Hg). Heparinization was adjusted to maintain activated clotting time 150-180 sec. MV (L/min), respiratory rate (RR), Hemolung blood flow (BF, L/min), CO_2 removal by the Hemolung ($V_{Hemolung}CO_2$, ml/min), PaO_2 and $PaCO_2$, plasma free hemoglobin (PfHb, g/dl), O_2 consumption by the lung (VO_2, ml/min), and CO_2 production by the lung ($V_{lung}CO_2$, ml/min) were measured at baseline, 2 hours after device insertion and every 6 hours thereafter.

Results

MV was reduced from 5.6 L/min at baseline to 2.6 L/min 2 hours after device insertion, and was maintained at 3 L/min+/- SEM until the end of the study.$V_{Hemolung}CO_2$ remained steady over 72 hours, averaging 72 ± 1.2 ml/min at blood flows of 447 ± 5 ml/min. After device insertion, VO_2 did not change; $V_{lung}CO_2$ decreased by 50% and stayed at that level ($p<0.001$). As the venous PCO_2 rose or fell, so did $V_{Hemolung}CO_2$. PfHb and ACT did not change.

Conclusions

V_2CO_2R by the Hemolung enabled a nearly 50% reduction in MV. V_2CO_2R may be an effective adjunct to or replacement for mechanical ventilation for example during en-route care for combat casualties.

1.0 INTRODUCTION

Acute respiratory distress syndrome (ARDS) has a 30-50% mortality, affects about 150,000 patients per year, and together with chronic lung failure causes 1 in every 7 deaths in the USA (1). Acute lung injury (ALI) and ARDS are also significant combat casualty care entities stemming from trauma and resuscitation (2,3); smoke inhalation and burns (4); pulmonary contusion (5); use of chemical weapons such as mustard agent (6) as well as blast injury (7). Toxic industrial chemicals such as chlorine can also lead to ARDS (8) and have been employed with improvised explosive devices in a recent conflict (9). Civilian events such as the current H1N1 pandemic have the potential to overwhelm the available pool of mechanical ventilators, thus signifying the need for alternative lung-support therapies.

Though it is the mainstay of current ALI/ARDS therapy, mechanical ventilation can itself lead to secondary ventilator-induced lung injury (VILI) (10-16). Low-tidal-volume lung-protective strategies in ARDS decreased inflammatory mediator levels (13,14), end-organ dysfunction (14,17) and mortality (14). Consequences of low-tidal-volume ventilation, however, may include cardiovascular instability, use of high fraction of inspired O_2 (FiO_2), hypoventilation, alveolar derecruitment, hypercarbia and acidosis, and have led to a search for better lung-protective approaches (1). In addition the low-tidal-volume strategy, though accepted as a standard of care for ARDS, has in clinical practice been implemented in a variable fashion (18-23).

An alternate approach to the treatment of acute respiratory insufficiency and an avenue for avoiding VILI and achieving "lung rest" is to perform gas exchange via an extracorporeal device.(24-28) (29,30). Extracorporeal membrane oxygenation (ECMO) has, to date, been too costly for routine use as a lung-rest strategy in adult ARDS patients. To this end, Zwischenberger and colleagues developed a less invasive arterio-venous CO_2 removal ($AVCO_2R$) system (26, 31, 32). $AVCO_2R$ requires an adequate cardiac output and blood pressure, as well as placement of an arterial catheter which may lead to limb ischemia (33).

The purpose of the current study was to investigate the lung replacement potential of a new motor-driven extracorporeal veno-venous carbon dioxide removal device (V_2CO_2R) that allows for CO_2 removal at relatively low blood flow rates (400-600 ml/min) (Hemolung, ALung Technologies Inc. Pittsburgh, PA). This technology has a high gas-exchange efficiency per membrane surface area (0.59 m^2). Invasiveness is reduced by use of a dual-lumen catheter and a single-stick venous approach. Operation is driven by a pump, which allows for use in low cardiac output states. We tested the ability of the Hemolung to reduce the need for ventilatory requirements in mechanically ventilated swine over 72 hours. We hypothesized that Hemolung would permit a significant reduction in minute ventilation while maintaining normocapnia.

2.0 MATERIALS AND METHODS

This study was approved by the US Army Institute of Surgical Research Animal Care and Use Committee and was carried out in accordance with the guidelines set forth by the Animal Welfare Act, other federal statutes and regulations, and by the 1996 *Guide for the Care and Use of Laboratory Animals* of the National Research Council.

2.1 Animal Preparation

Seven female Yorkshire pigs weighing 54.2 $\pm$ 0.8 kg SEM were fasted for 24 hours, anesthetized with isoflurane (2-4 Volume %) via a mask and intubated. Next, total intravenous anesthesia (ketamine 200-500 mcg/kg/min and midazolam 2-5 ml/hr) was started through an ear vein and femoral arterial and venous catheters were aseptically placed for blood-pressure monitoring, intravenous access, and sample collection. The animals were volume-control ventilated using a Siemens Servo 300A ventilator (Siemens-Elema AB, Sweden) with room air at a tidal volume (TV) of 12 ml/kg and respiratory rate (RR) of 8-9 per minute. RR was adjusted at baseline to maintain normocapnia ($PaCO_2$ 35-45 mm Hg). Each animal received a maintenance rate of lactated Ringers' solution (LR) to maintain urine output at 0.5-1 ml per kg body weight per hour.

2.2 Hemolung Description and Insertion

The Hemolung system consists of a unit in which gas exchange takes place (Fig. 1, A) and an integrated control console (Fig. 1, B). The system is interfaced with the patient through a custom dual-lumen 15-Fr. catheter similar to a dialysis catheter. The catheter is designed to offer low flow resistance and superior kink resistance compared to off-the-shelf dialysis catheters (Fig. 1 C). The Hemolung pump withdraws venous blood from the superior vena cava which, after CO_2 removal, is re-infused in to the right atrium through the distal openings. Inside the Hemolung unit blood flows centrally into a rotating core, is radially pumped through a stationary annular fiber bundle, and returns to the patient via an outlet port (Figure 1, A). Unlike conventional passive oxygenators, the core utilizes a motor-driven rotational motion to increase gas-exchange efficiency. This increases the amount of CO_2 removed relative to the surface area (0.59 m^2) of the fiber bundles. This increased efficiency permits blood-flow rates comparable to those used in dialysis (300-600 ml/min).

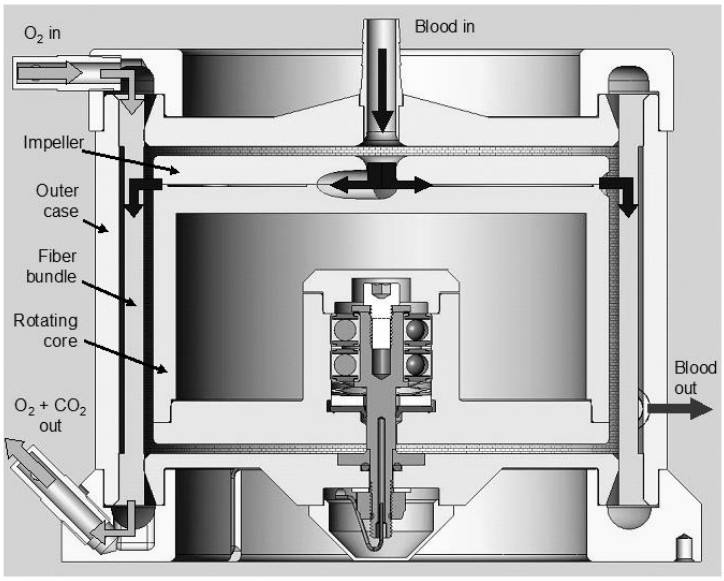

Figure 1 (a): Hemolung unit.

Figure 1 (b): Controller.

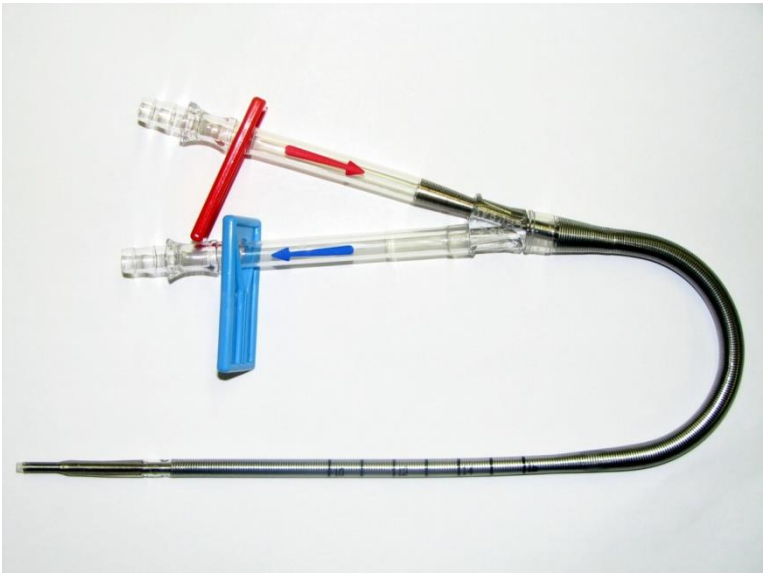

Figure 1 (c): Dual lumen catheter.

After 1 hour of baseline stabilization, the Hemolung unit was primed with 300 ml of normal saline containing 5000 u of heparin. The right jugular vein was aseptically exposed via a cut down. After a 20 u/kg intravenous bolus of heparin, each animal underwent placement of the 15 Fr. catheter through the external jugular vein.

The catheter was positioned so that the proximal set of openings was situated in the superior vena cava and the distal tip (with another set of openings) was placed in the right atrium. Plastic tubing provided by the manufacturer was immediately connected to each of the two ports of the catheter using the wet-to-wet technique and the Hemolung unit was started. Placement of the catheter was confirmed via fluoroscopy.

After device insertion, the ventilator settings were reduced according to an algorithm in order to maintain normocarbia. First, RR was reduced to the minimum setting allowed by the ventilator (5 breaths/per minute) and kept there unless hypercarbia developed. Further decreases in MV were sought via reduction in TV in 2 ml/kg steps as verified by blood gas analysis. TV and RR were adjusted if the combined effects of Hemolung and ventilator were inadequate to maintain normocarbia. Animals were maintained for 72 hours with round-the-clock care in an animal ICU.

2.3 Measurements

Heparin was given continuously during the study and assessed by the activated clotting time (ACT, sec) using a Hemochron Jr. Whole Blood Microcoagulation System (ITC Europe, Rodano, Italy). Heart rate (HR, beats per minute), systolic arterial pressure (SAP), minute ventilation (MV, L/min), respiratory rate (RR, breaths/minute), and tidal volume (TV, ml/min) were recorded. Oxygen consumption (VO_2, ml/min) and carbon dioxide production ($V_{lung}CO_2$, ml/min) were measured using a Deltatrac II metabolic cart (Sensor Medics, Yorba Linda, CA) and adjusted for body surface area. Hemolung blood flow (BF, L/min), $V_{Hemolung}CO_2$ removal (CO_2 rem., ml/min) and sweep gas flow (ml/min) were recorded from the Hemolung console (ALung Technologies, Inc., Pittsburgh, PA). Arterial tension of oxygen (PaO_2, mm Hg) and carbon dioxide ($PaCO_2$, mm Hg) were measured at baseline, 2 hours after insertion of the Hemolung and every 6 hours thereafter (Roche, CO Bas B 221, Indianapolis, IN). Plasma free hemoglobin (PfHb, g/dl) was determined using spectrophotometry (34).

2.4 Statistical Analysis

Statistical analysis by one-way ANOVA with repeated measures and adjustment for multiple comparisons was performed using SAS v. 9.1. (Cary, NC). Significance was accepted at $p<0.05$.

3.0 RESULTS

A total of 504 hours of ICU care were performed in the conduct of this study. MV and RR decreased 2 hours after device placement and remained reduced to 50% of baseline value throughout the duration of the study (Table 1, Fig 2). TV was about 100 to 75 ml lower at each time point compared to baseline values, but these changes were not significant. PaO_2 was lower at 2 hours, whereas $PaCO_2$ was higher at 48 and 72 hours after insertion when compared to baseline values (Table 1). The pH was unchanged throughout the study. Average CO_2 removal ($V_{Hemolung}CO_2$) over the entire study duration was 72 ± 1.2 ml/min. It remained not different from baseline at all time points, other than at the 72-hour time point when it decreased to a mean of 65 ml/min (Table 1, Fig. 3). Mean BF over the study was 447 ± 5 ml/min and remained steady (Table 1). Revolutions per minute of the motor remained steady in the 1200 to 1300 range throughout the 72 hours (data not shown). Sweep gas flow averaged 8.6 L/min throughout the study (data not shown). HR and SAP did not change after placement of the Hemolung unit at any time, except at 24 hours after Hemolung placement when HR decreased from 100 to 77 beats/min (Table 2). VO_2 did not change, whereas $V_{lung}CO_2$ decreased significantly at all time points after device placement to nearly half of the baseline value (Table 2). ACT remained unchanged throughout the study. The PfHb levels remained steady and low throughout the duration of the study (Table 2).

Table 1: Ventilatory data, blood gas data, and key Hemolung parameters. MV, minute ventilation (liters per minute); RR, respiratory rate (breath per minute); TV, tidal volume (milliliters per minute); PaO_2, partial pressure of oxygen in arterial blood (mmHg); PCO_2, partial pressure of carbon dioxide in arterial blood (mmHg); pH, hydrogen ion concentration in arterial blood (relative units); CO_2 removal, carbon monoxide removal by the Hemolung device (milliliters per minute); BF, blood flow through the Hemolung device (milliliters per minute). All data are means ± SEM. Statistics by one-way ANOVA with repeated measures and adjustment to multiple comparisons. *Significant difference vs. baseline at p<0.05.

Variables	Baseline	2 hr	24 hr	48 hr	72 hr	p, BL vs. 2 hr	p, BL vs. 24 hr	p, BL vs. 48 hr	p, BL vs. 72 hr
MV, L/min	5.6 ± 0.3	2.6 ± 0.3*	3.0 ± 0.1*	3.1 ± 0.2*	3.3 ± 0.2*	0.02	0.0004	0.0003	0.0002
RR, breath/min	9	5*	5*	5*	5*	0.0002	0.0004	0.001	0.003
TV, ml	650 ± 14	556 ± 24	576 ± 9	574 ± 15	578 ± 15	0.087	0.084	0.16	0.18
PaO_2, mm Hg	96 ± 2	77 ± 5*	103 ± 8	97 ± 16	112 ± 8	0.04	0.94	0.55	0.08
$PaCO_2$, mm Hg	39 ± 0.8	43 ± 2.2	42 ± 1.0	44 ± 1.2*	46 ± 5.8*	0.52	0.08	0.01	0.0003
pH	7.46 ± 0.0	7.41 ± 0.0	7.47 ± 0.0	7.45 ± 0.0	7.44 ± 0.0	0.14	0.98	1.0	0.99
CO_2 removal, ml/min	n/a	76 ± 3.0	73 ± 1.2	69 ± 2.7	65 ± 2.6*	n/a	0.62	0.17	0.03
BF, ml/min	n/a	422 ± 11	471 ± 24	445 ± 29	431 ± 21	n/a	0.42	0.77	0.67

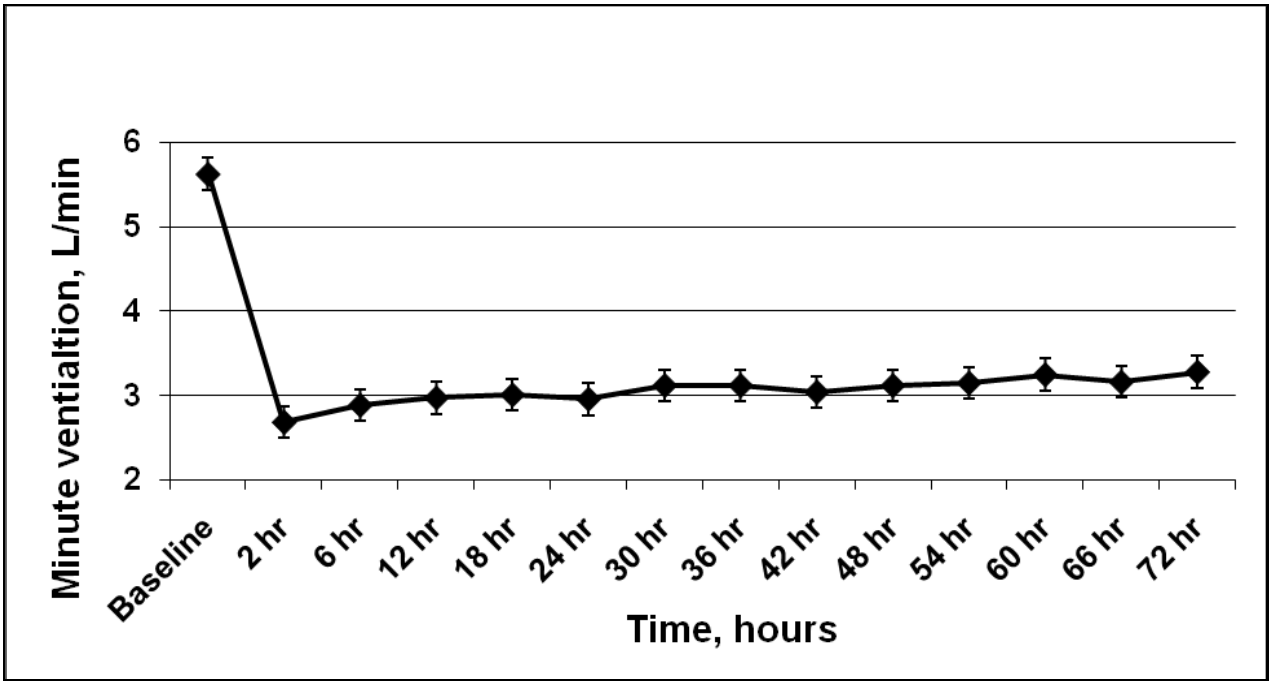

Figure 2: Changes in minute ventilation (for statistical significance, see Table 1).

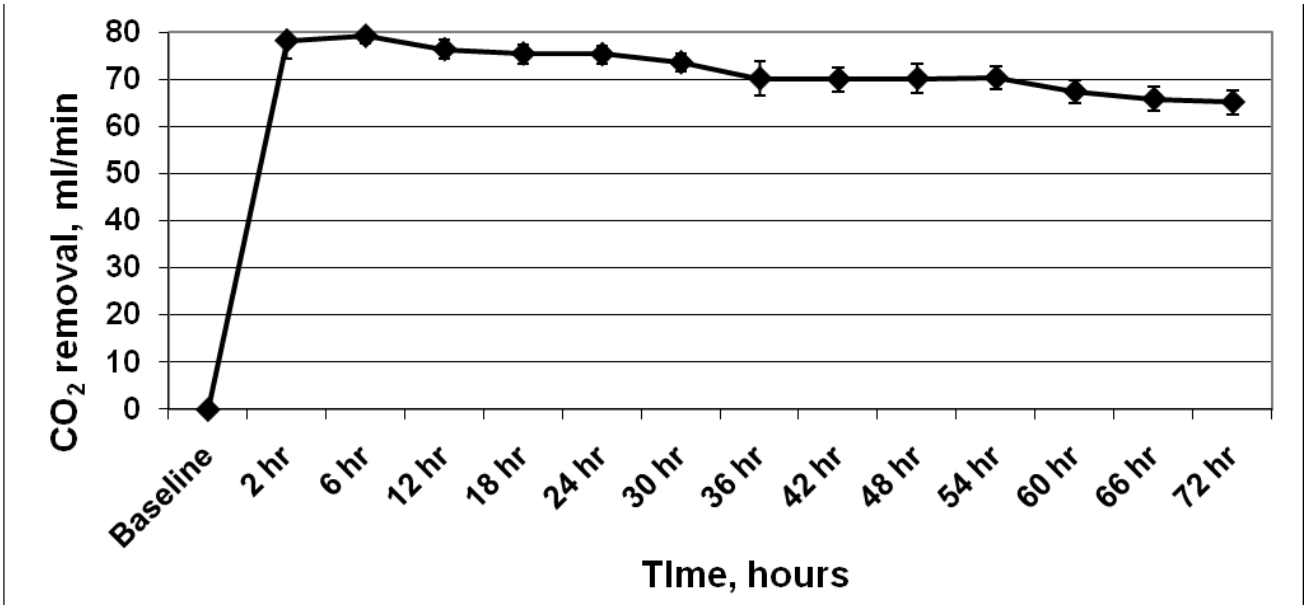

Figure 3: Changes in CO_2 removal (for statistical significance, see Table 1).

Table 2: Hemodynamic, metabolic and data. HR, heart rate (beat per minute); SAP, systolic arterial pressure (mmHg); VO_2 oxygen consumption (milliliters per minute); VCO_2, carbon dioxide production (milliliters per minute); PfHb, plasma free hemoglobin (milligrams per deciliter); ACT, activated clotting time (seconds). All data are means ± SEM. Statistics by one-way ANOVA with repeated measures and adjustment to multiple comparisons. *Significant difference vs. baseline at p<0.05.

Variables	Baseline	2 hr	24 hr	48 hr	72 hr	p, BL vs. 2 hr	p, BL vs. 24 hr	p, BL vs. 48 hr	p, BL vs. 72 hr
HR, beats/min	100 ± 11	86 ± 11	77 ± 6 *	89 ± 9	84 ± 6	0.23	0.02	0.49	0.89
SAP, mm Hg	130 ± 8	125 ± 6	117 ± 6	114 ± 11	117 ± 15	0.99	0.55	0.46	0.50
VO_2, Ml/min	313 ± 37	320 ± 39	259 ± 26	277 ± 33	262 ± 31	0.98	0.09	0.56	0.06
VCO_2, ml/min	262 ± 27	135 ± 15*	141 ± 13*	152 ± 17*	147 ± 18*	0.0005	<0.0001	<0.0001	<0.0001
PfHb, mg/dL	14.6 ± 2.4	10.5 ± 1.5	17.6 ± 5.8	10.9 ± 1.8	16.6 ± 2.8	0.81	0.99	0.76	0.98
ACT, sec	106 ± 4	186 ± 25	141 ± 24	150 ± 22	135 ± 25	0.10	0.69	0.44	0.57

4.0 DISCUSSION

The main finding of this study is that use of a novel veno-venous CO_2 removal device (Hemolung) in healthy swine allowed for a significant reduction in minute ventilation which was sustained for 72 hours. Unlike passive oxygenators which rely on the arterio-venous pressure gradient and require both arterial and venous cannulation for gas exchange (30,35), the Hemolung system utilizes a single-stick dual-lumen venous cannula

and an extracorporeal rotational motor. This motor, by increasing blood flow across the fibers, allows for optimized CO_2 elimination for a membrane surface area of $0.59m^2$. Increased gas exchange efficiency in the Hemolung permits use of lower blood flow rates in the 300-750 ml/min range, compared to 800-1500 ml/min in the current $AVCO_2R$ devices (26, 30, 35, 36).

Despite heparin coating of current gas exchangers one of the continuing limitations in extracorporeal lung use is the requirement for systemic heparin administration. The present study did not pursue the minimal possible dose of heparin usable with the Hemolung. Although the fibers are Siloxane coated to reduce thrombogenicity, manufacturer recommendations called for maintenance of ACT around 180 sec. One of the units developed a thrombus inside due to a structural defect in the fibers, but continued to perform without a decline in CO_2 elimination. The levels of plasma free hemoglobin--a measure of erythrocyte vulnerability to shear stress--did not change over the experiment signifying safe operational conditions over 72 hours.

Artificial lung support systems are medical devices designed to supplement or replace the respiratory function of the natural lung. Extracorporeal membrane oxygenation (ECMO) gained acceptance for treatment of neonatal respiratory failure (37). But it is currently used in adults only in select tertiary-care centers, requires highly trained staff and meticulous patient selection, and is considered complicated and costly (38,39). Gattinoni and colleagues described extracorporeal CO_2 removal for the treatment of patients with severe respiratory failure in 1986 (40). Alpard and Zwischenberger developed an extracorporeal arterio-venous CO_2 removal ($AVCO_2R$) system using a low resistance ECMO oxygenator for gas exchange, and showed that it permitted reduction in minute ventilation, reduced airway pressure, improved PaO_2-to-FiO_2 ratio, and improved survival in animal models of ARDS(24,26-28,35). Another $AVCO_2R$ device, marketed in Europe as the Interventional Lung Assist device (Novalung), has also shown promise as a means for lung rest (29,41). Compared to the Hemolung, currently available $AVCO_2R$ devices require a higher blood flow (500-1500 ml/min), and carry a risk of limb ischemia due to arterial cannulation (33).

The results of our work add to the growing number of reports that found partial extrapulmonary CO_2 removal a form of lung-protective strategy via reduction in ventilatory settings. The study by Cardenas using V_2CO_2R is of particular relevance to our work as it employed a modified veno-venous CO_2 removal approach, a single-stick dual-lumen catheter, and a pump (42). In that study, however, a modified ECMO system was used. At comparable blood flows (500 ml/min), it achieved only half the CO_2 removal (31 ml/min) we observed in the present study. Optimization of CO_2 removal in the Cardenas study was achieved by doubling the blood flow at 1000 ml/min and a 15 L/min sweep gas flow (twice the settings of the present study), reaching 150 ml/min of CO_2 elimination (42). Recently a unique veno-venous CO_2-removal approach was tested in humans with ARDS, in which a pediatric ECMO system (membrane surface area $0.33m^3$) was connected in series with a dialysis circuit (43). Tidal volumes were reduced below the 6 ml/kg ARDSnet recommended target, and the resulting respiratory acidosis was successfully managed via the extracorporeal circuit. The authors concluded that their CO_2-removal system allowed for safe use of lower-than-customary tidal volumes (43).

Our study highlights several distinguishing features of the Hemolung when compared to existing devices. These features argue in favour of potential applicability of the Hemolung during en-route care for mechanically ventilated combat casualties with acute lung injury. First, in the present study a 15-Fr. dual-lumen catheter was used which is smaller than most currently used catheters, and permits for a single-stick venous insertion. Avoidance of arterial cannulation is a benefit of this system as it lowers the risk of lower limb ischemia, hemorrhage and systemic thromboembolism. Second, Hemolung insertion and function did not lead to hemodynamic changes as neither heart rate nor blood pressure changed clinically significantly at any time during the experiment. The above features may extend the applicability of this technology to casualties with hemorrhagic shock and trauma. Third, the Hemolung is battery-operated, portable and can be wheeled

around with the patient using only ambient air for sweep gas and CO_2 removal. These features may make it amenable for use during aero-medical evacuation.

CO_2 removal rates were steady and efficient over the course of the experiment, especially considering the low blood flow rates used. In general CO_2 removal is a function of 3 conditions: 1) PCO_2, in that an increase in PCO_2 leads to an increase in VCO_2; 2) sweep gas flow rate (regulated by the user); and 3) blood flow through the device (a function of the catheter size and the device RPM). Because higher RPMs may lead to hemolysis, more efficient gas exchange at lower rates is a desirable alternative. The current study sought to use the Hemolung in conjunction with mechanical ventilation to achieve a "normal" blood gas, defined as arterial oxygen saturation of above 92% and $PaCO_2$ tension of 35-45 mm Hg. Whereas the absence of clinical hypercarbia in the study design limited our ability to explore maximal CO_2 elimination, in bench studies conducted by the Hemolung developers (44) theVCO_2 capacity of the prototype Hemolung was estimated to be 250 ml/min/m^2 at 1500 RPMs assuming a membrane with a 0.4 m^2. We expect to challenge the Hemolung for its maximal CO_2 removal capacity in a follow-up study involving animals with ARDS.

5.0 CONCLUSIONS

In summary, use of the Hemolung for veno-venous CO_2 removal in an uninjured porcine model allowed a significant and sustained reduction in minute ventilation while maintaining normocapnia. The system performed about 50% of ventilatory function via percutaneous venous cannulation with a dual-lumen catheter similar to a dialysis catheter. Gas exchange efficiency was maintained for 72 hours at low flow rates. No pronounced hemodynamic effects upon insertion and operation were observed. Overt erythrocyte destruction, manifested by plasma free hemoglobin levels, was absent. This approach may augment treatment options for patients with various forms of respiratory failure ranging from ARDS, to COPD patients with acute exacerbation, and patients awaiting lung transplant. Because of its ease of use, Hemolung may also make it possible to more rapidly initiate extracorporeal lung support in emergency departments, community hospitals as well as during en-route care and air-evacuation of combat casualties to continental US.

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